REMARKS

This paper is being submitted in response to the Office Action dated January 7, 2003 (*PTO Paper No. 13*), wherein the Examiner (1) withdraws the restriction requirement with respect to the inventions of Groups I (claims 1-8 and 11) and III (claims 13-15), and maintains the restriction requirement with respect to the inventions of Groups II (claims 9 and 10), IV (claims 14-16), V (claims 18, 28, and 29), VI (claims 19 and 20), VII (claims 19 and 20), VIII (claims 21 and 23), and IX (claims 26 and 27), both to each other and to the invention of Group I (now including claims 1-8, 11, and 13-15); and (2) rejects claims 1-8, 11, and 13-15 as being unpatentable under either 35 U.S.C. § 102(a), 35 U.S.C. § 102(b), or 35 U.S.C. § 103(a).

With regard to item (1), Applicant thanks the Examiner for withdrawing the restriction requirement with respect to the inventions of Groups I and III. However, Applicant disagrees with the Examiner's maintenance of the restriction requirement with respect to the inventions of Groups V (claims 18, 28, and 29) and IX (claims 26 and 27), both to each other and to the invention of Group I (now including claims 1-8, 11, and 13-15). Accordingly, Applicant has separately filed with the Commissioner for Patents a Petition Under 37 C.F.R. § 1.144 for Review of Requirement for Restriction. A copy of this Petition is attached.

Applicant notes that two previous versions of this paper have been filed. The first was filed on May 7, 2003, but was deemed by the Examiner – in an Office Action dated June 26, 2003 – to fail to comply with the requirements set forth in 37 C.F.R. § 1.121. However, because the Examiner deemed this paper to constitute a bona fide response, Applicant was given one month or 30 days (whichever is longer) to submit a paper in compliance with 37 C.F.R. § 1.121 in order to avoid abandonment of the captioned application. In response, Applicant submitted on July 7, 2003 a revised version of its May

7, 2003 paper. However, in an Office Action dated October 7, 2003, the Examiner indicated that Applicant's July 7, 2003 paper was also not in compliance with 37 C.F.R. § 1.121. Once again, the Examiner deemed this paper to constitute a bona fide response, and therefore gave Applicant one month or 30 days (whichever is longer) to submit a paper in compliance with 37 C.F.R. § 1.121 in order to avoid abandonment of the captioned application. The current paper, then, is being submitted in response to the October 7, 2003 Office Action.

Rejections Under 35 U.S.C. § 102(a)

The Examiner rejects claims 1, 2, 6, and 11 as unpatentable under 35 U.S.C. § 102(a) due to being anticipated by each of Timmermann *et al.*, *Kidney Intl.* 53:1455-60 (June 1998) ("Timmerman #1") and Timmerman *et al.*, *J. Molecular Med.* 76:B30, Abst. P-109 (May 1998) ("Timmerman #2").

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred prior to the effective date of either of these references. Applicant therefore respectfully requests the withdrawal of this rejection.

Rejections Under 35 U.S.C. § 102(b)

The Examiner rejects claims 13 and 14 as unpatentable under 35 U.S.C. § 102(b) due to being anticipated by Intl. Publ. No. WO 97/35973.

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred

prior to the effective date of this reference. Applicant therefore respectfully requests the withdrawal of this rejection.

Next, the Examiner rejects claims 13-15 as unpatentable under 35 U.S.C. § 102(b) due to being anticipated by each of (1) GenBank Accession No. Y00106 (Sept. 12, 1993), and (2) Emorine *et al.*, *Proc. Natl. Acad. Sci. USA* 84:6995-9 (Oct. 1987) ("Emorine"). Although not acceding to the Examiner's rejection, Applicant notes that claim 13 has been amended herein to recite the fact that the composition comprises at least one allele-specific oligonucleotide (ASO) that hybridizes to a β_2AR polynucleotide at a region containing the 5'LC polymorphic site, *wherein the ASO is not less than 10 nucleotides in length and not more than 100 nucleotides in length*. Support for the amendment of claim 13 herein can be found, *inter alia*, at page 9, line 4 – page 12, line 2. Because the polynucleotide sequences disclosed in GenBank Accession No. Y00106 and in the Emorine reference are well in excess of 100 nucleotides, neither of these references anticipates claim 13 as amended. As such, Applicant respectfully requests the withdrawal of this rejection.

Rejections Under 35 U.S.C. § 103(a)

The Examiner rejects claims 1, 2, 6-8, 11, 13, and 15 under 35 U.S.C. § 103(a) due to being rendered obvious by Timmermann *et al.*, *Kidney Intl.* 53:1455-60 (June 1998) (Timmerman #1) in view of Green *et al.*, *Amer. J. Resp. Cell Mol. Biol.* 13:25-33 (July 1995) ("Green") and the Emorine reference.

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred

prior to the effective date of the Timmerman #1 reference. Applicant therefore respectfully requests the withdrawal of this rejection.

Next, the Examiner rejects claims 1, 2, 6-8, 11, 13, and 15 under 35 U.S.C. § 103(a) due to being rendered obvious by the Timmerman #2 reference in view of the Green reference and the Emorine reference.

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred prior to the effective date of the Timmerman #2. Applicant therefore respectfully requests the withdrawal of this rejection.

Next, the Examiner rejects claims 1, 2, 6-8, 11, 13, and 15 under 35 U.S.C. § 103(a) due to being rendered obvious by Timmermann *et al.*, *Human Mutation* 11(4):343-4 (March 1998) ("Timmerman #3") in view of the Green reference and the Emorine reference.

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred prior to the effective date of the Timmerman #3 reference. Applicant therefore respectfully requests the withdrawal of this rejection.

Next, the Examiner rejects claims 1, 2, 4-6, 11, 13, and 14 under 35 U.S.C. § 103(a) due to being rendered obvious by the Timmermann #1 reference in view of United States Patent No. 5,817,477 ("'477 patent").

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred prior to the effective date of the Timmerman #1 reference. Applicant therefore respectfully requests the withdrawal of this rejection.

Next, the Examiner rejects claims 1, 2, 4-6, 11, 13, and 14 under 35 U.S.C. § 103(a) due to being rendered obvious by the Timmermann #2 reference in view of the '477 patent and the Emorine reference.

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred prior to the effective date of the Timmerman #2 reference. Applicant therefore respectfully requests the withdrawal of this rejection.

Next, the Examiner rejects claims 1, 2, 4-6, 11, 13, and 14 under 35 U.S.C. § 103(a) due to being rendered obvious by the Timmermann #3 reference in view of the '477 patent and the Emorine reference.

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred prior to the effective date of the Timmerman #3 reference. Applicant therefore respectfully requests the withdrawal of this rejection.

Next, the Examiner rejects claims 1-3, 6, and 11 under 35 U.S.C. § 103(a) due to being rendered obvious by the Timmermann #3 reference in view of Large *et al., J. Clin. Invest.* 100:3005-13 (Dec. 1997) ("Large") and the Emorine reference, and further in view of New England BioLabs Catalog, p. 38 (1995) ("NEB Catalog").

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred prior to the effective date of the Timmerman #3 reference. Applicant therefore respectfully requests the withdrawal of this rejection.

Next, the Examiner rejects claims 1-3, 6, and 11 under 35 U.S.C. § 103(a) due to being rendered obvious by the Timmermann #2 reference in view of the Large reference and the Emorine reference, and further in view of the NEB Catalog reference.

In response to this rejection, Applicant submits herewith a Declaration of Prior Invention Under 37 C.F.R. § 1.131, demonstrating that the invention(s) embodied in these claims occurred prior to the effective date of the Timmerman #2 reference. Applicant therefore respectfully requests the withdrawal of this rejection.

Finally, the Examiner rejects claims 1 and 11 under 35 U.S.C. § 103(a) as unpatentable due to being rendered obvious by the Emorine reference in view of the '477 patent and United States Patent No. 6,087,485 ("'485 patent").

More specifically, the Examiner asserts that:

> Emorine teaches methods of sequencing the β2-AR gene and teachings [sic] the resulting sequence of the β2-AR gene including the leader cistron sequences.
>
> Emorine does not teach determining the sequence of both copies of the β2-AR gene.
>
> However, . . . [the '485 patent] teaches methods for detecting sequencing genomic DNA and for determining the presence of mutations and polymorphisms in DNA. IN [sic] the method of . . . [the '485 patent], genomic DNA is amplified by PCR, cycle sequencing is performed, and sequences are determined and analyzed for the presence of heterozygous positions. The method of . . . [the '485 patent] results in the analysis of the sequence of both copies of a genomic DNA sequence. Furthermore, . . . [the '477 patent] teaches the importance of determining the sequence of adrenergic receptor genes and of identifying the sequence variations in the adrenergic receptor genes.
>
> In view of the teachings of ... [the '485 patent and the '477 patent], it would have been obvious to one of ordinary skill in the art at the time the invention was made
>
> to have analyzed the β2-AR gene using the cycle sequencing method of . . . [the '485 patent] in order to have provided an effective means for analyzing the β2-AR gene for the presence of genetic variation. Such a method would have analyzed all positions of the β2-AR gene including the –47 5' LC polymorphic

> site and would have necessarily identified the nucleotide pair present at the 5' LC polymorphic site.

PTO Paper No. 13, pp. 20-21 (internal citations omitted).

Applicant respectfully disagrees with the Examiner's analysis. In order to establish a *prima facie* case of obviousness, the Examiner must establish three facts. First, the Examiner must establish that there exists some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, the Examiner must establish that there exists a reasonable expectation of success. Finally, the Examiner must establish that the prior art reference (or references when combined) teaches or suggests all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Without regard to whether the first two *Vaeck* criteria have been established, Applicant notes that the references – taken either individually or together – do not teach or suggest all the claim limitations of claims 1 and 11. Applicant has discovered the existence of DNA sequence variation with respect to the region upstream of the human β_2AR gene. Applicant has discovered that this variation occurs at a position 47 base pairs upstream of the coding region of the β_2AR gene, which begins at nucleotide position 1588 of SEQ ID NO:1. Applicant has, throughout the specification, defined this position as the "5' leader cistron polymorphic site." However, while the cited references may, in combination, teach or suggest a method for looking for polymorphic sites in the β_2AR gene, these references do not – taken either individually or together – teach or suggest a claim directed to genotyping the β_2AR gene of an individual comprising determining the identity of the nucleotide pair at a specific polymorphic site, namely

the 5' leader cistron polymorphic site in the two copies of the β_2AR gene present in the individual. As such, the Examiner has not established a *prima facie* case of obviousness of claims 1 and 11 as filed and the rejection should be withdrawn.

Notwithstanding the foregoing, Applicant has, in an effort to expedite prosecution, amended claim 1 to merely clarify that the claimed method is indeed directed to determining the identity of the nucleotide pair at a specific β_2AR polymorphic site, which is not taught or suggested by the prior art, by reciting in the claim the nucleotide pairs that the specification states exist at that site, i.e., (a) cytosine and cytosine; (b) cytosine and thymine; and (c) thymine and thymine. Support for the amendment of claim 1 herein can be found, *inter alia*, at page 3, lines 18-28.

CONCLUSION

As mentioned above, two previous versions of this paper have been filed. The first was filed on May 7, 2003, but was deemed by the Examiner – in an Office Action dated June 26, 2003 – to fail to comply with the requirements set forth in 37 C.F.R. § 1.121. However, because the Examiner deemed this paper to constitute a bona fide response, Applicant was given one month or 30 days (whichever is longer) to submit a paper in compliance with 37 C.F.R. § 1.121 in order to avoid abandonment of the captioned application. In response, Applicant submitted on July 7, 2003 a revised version of its May 7, 2003 paper. However, in an Office Action dated October 7, 2003, the Examiner indicated that Applicant's July 7, 2003 paper was also not in compliance with 37 C.F.R. § 1.121. Once again, the Examiner deemed this paper to constitute a bona fide response, and therefore gave Applicant one month or 30 days (whichever is longer) to submit a paper in compliance with 37 C.F.R. § 1.121 in order to avoid abandonment of the

captioned application. The current paper, then, is being submitted in response to the October 7, 2003 Office Action.

Applicant reiterates that this response is being filed after the shortened statutory deadline for responding to the January 7, 2003 Office Action (April 7, 2003), but on or prior to one month following this deadline (May 7, 2003). Therefore, Applicant respectfully requests a one-month extension of time under 37 C.F.R. § 1.136(a), thereby extending the response period to May 7, 2003. Applicant authorizes the Commissioner to deduct the requisite fee for this extension ($110.00; see 37 C.F.R. § 1.17(a)(2)) from Deposit Account No. 50-1293.

Respectfully submitted,

Matthew M. Catlett
Registration No. 44,067
Genaissance Pharmaceuticals, Inc.
Five Science Park
New Haven, CT 06511
203.776.1450
203.492.4474 (fax)